UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/484,786	06/07/95	MACH B	MACH-2-CONT.

HM31/0428

JAMES F HALEY JR
FISH & NEAVE
1251 AVENUE OF THE AMERICAS
NEW YORK NY 10020-1104

EXAMINER	
ARTHUR, L.	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 04/28/98

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary	Application No. 08/484,786	Applicant(s) Mach et al.
	Examiner Lisa Arthur	Group Art Unit 1634

☒ Responsive to communication(s) filed on *Jan 3, 1998*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *16, 17, 20, 23-42, 44, 46, 47, 49, and 50* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *16, 17, 20, 23-42, 44, 46, 47, 49, and 50* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6,12*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This action is in response to the papers filed under 37 C.F.R. 1.129(a) on January 30, 1998. Currently, claims 16,17, 20, 23-42, 44, 46,47,49 and 50 are pending in this application. All of the amendments and arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action contains new grounds of rejection. The current status of the pending claims is as follows:

I. Claims 16,17,20,23,24,26-37,40-42,44,46,47,49 and 50 are rejected under 35 U.S.C. 112, first paragraph, new matter.

II. Claims 16,17,20,23,24,26-37,40-42,44,46,47 and 49-50 stand rejected under 35 U.S.C. 112, first paragraph, scope.

III. Claims 17,17,20,22-42,44,46,47 and newly added claims 49 and 50 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of US Pat 5,169,941.

IV. Claims 16,17, 20, 23-42, 44, 46,47,49 and 50 are rejected under 35 U.S.C. 112, first paragraph.

V. Claims 16,17, 20, 23-42, 44, 46,47,49 and 50 are rejected under 35 U.S.C. 112, second paragraph

VI. Claims 23,24,26-29,31-33,36,37 are rejected under 35 U.S.C. 102(b).

VII. Claims 16,17,20,30,40,41,42,44,46,47,49,50 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 5,503,976.

NEW MATTER

2. Claims 16,17,20,23,24,26-37,40-42,44,46,47,49 and 50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A) Claims 16,17,20,23,24,26-30,34-36,44,46 and 49 are rejected over the language "specifically hybridize" and over DNA sequences which code for a portion comprising a region of mismatch between any two of the "foregoing" sequences (step (d) in claim 23, for example). The specification does not support these concepts because the specification does not define "specifically hybridize" and does not teach the concept of making DNA sequences of any size that

generally contain regions of mismatch. First, since the term "specifically hybridize" is not used in the specification, the intended meaning of this term the regard to the instant claims is unclear. Specifically hybridize is usually considered to mean that a DNA sequence hybridizes only to another specifically named DNA sequence. However, in this case the specification teaches the isolation and cloning of at most 4 DR-B chain genes, the nucleotide and predicted amino acid sequences of two of those genes, A and B. The specification teaches that DR-b clones from a cell line called IBW-9 by hybridizing a DR-B clone isolated from a Raji et al cell line. The specification states at the bottom of page 26 continuing to the top of page 27 that the DR-B-A,B,C, and D inserts can be used to isolate other B-chain families by "high criterium hybridization". Since the specification does not use the term "specifically hybridize", the intended meaning of the term appears to be equivalent to that of "high criterium hybridization" which does not appear to mean that each insert or fragment of that insert hybridizes only with the DR-A, B, and C genes. Therefore, since "specifically hybridize" can be interpreted to mean that the DNA sequence would only hybridize to the specifically recited sequences, and since the specification does not teach that such "specificity" actually occurs even under high criterium hybridization, this concept is not supported by the specification and the amendment introduces new matter into the claims.

Second, the specification does not support DNA sequences which code for portions of a polypeptide that contains a region of mismatch between any two of the large number of DNA sequences claimed previously because the specification does not describe generally comparing

DR-B chain sequences to identify regions of mismatch and to then generate DNA sequences which contain those mismatches where the sequence can be any length and are not limited to a particularly disclosed DNA sequence. Instead, the specification specifically describes a comparison of DR-B-A and DR-B-B to identify three specific regions containing mismatches and one region which was conserved. The specification then teaches making short 19-mers spanning this mismatch containing region to distinguish between perfectly matching sequences from mismatching sequences (pages 31-32) by hybridization as a means for HLA-DR typing. These teachings , however, do not support the broader concept of aligning any two DNA sequences which can hybridize to the disclosed sequences to identify regions of mismatch and to method make DNA sequences of any length which contain those mismatch regions because the teachings in the specification are very specific, i.e. only the mismatches between DR-B-A and DR-B-B are taught and only 19-mer oligonucleotides containing the specifically identified mismatch regions were made. Therefore, this embodiment of the claims is new matter.

B) Claims 31,32,40-42,44,47 and 50 contain new matter because the claims are drawn to DNA sequences which specifically hybridize to the polymorphic regions between DR-A and DR-B to allow determination of HLA alleles for use in DR-B which the specification does not describe. The specification only describes the three mismatch regions between DR-B-A and DR-B-B and does not teach the concept of making and using DNA sequences that "specifically hybridize" to these polymorphic regions. There is no description in the specification that such DNA sequences were part of the originally filed invention and nothing in the specification

directing the artisan to look for such sequences. Instead the specification only describes two types of HLA typing methods, RFLP analysis using the specifically disclosed B-chain gene sequences and fragments as a probe or an improved method using 19-mer oligonucleotides which span the identified mismatch regions in a hybridization assay to distinguish perfect matches from imperfect matches. The specification is limited to describing the synthesis and use of these short 19.mer oligonucleotides that span the specific mismatch. At the time the invention was made allele specific oligonucleotides were limited to being short oligonucleotide as taught by Connor et al. (The reference cited at the bottom of page 39 of the specification.) The claims are also not supported by the specification because of the recitation of "specifically hybridizing" for the same reasons as given above in para. (A).

C) Claims 33,36,37,40,41,42,44 and 47 are contain new matter because they are drawn to DNA sequences that specifically hybridize DR-B and to the conserved region at amino acids 39-45 and which allow the determination of one or more HLA alleles for typing which concept is not taught by the specification. First, as discussed above "specifically hybridizing" sequences are not supported by the specification for the reasons given above. Second, the specification only teaches that the region between amino acids 39-45 of the disclosed B-chain genes is conserved between the specific DR-B chain gene sequences described in the specification and teaches one 19-mer which spans this region for use as a hybridization control in the improved HLA typing method. Since the specification teaches that the conserved region is present in all the DR-B chains tested,

and that the sequence was useful as a positive control, the specification does not describe or imply that this sequence would be useful for determining HLA alleles since all alleles would be expected to contain this sequence. The specification does not describe that the invention includes any sequence which contains or is complementary to this conserved region because the specification teaches that this sequence is present in DC genes and SB-beta chains which are encompassed by the claims as written but do not appear to be part of the intended invention (see page 32, para. 1).

WITHDRAWN REJECTIONS

3. The rejections of claims 23,24 and 31 previously made under 35 U.S.C. 112, second paragraph have been obviated by amendment

MAINTAINED REJECTION

4. Claims 16,17,20,23,24,26-37,40-42,44,46,47 and 49-50 stand rejected under 35 U.S.C. 112, first paragraph, for the reasons of record.

The response traverses the rejection on the following grounds. The response argues that the skilled artisan could use the instant specification to make the large number of sequences claimed using routine experimentation because the artisan would know that the useful DNA sequences are those that selectively hybridize and that determination of length is routine. The response alleges that once applicants identified the polymorphic and conserved region between DR-BA and DR-B-B, they also "made possible" sequences encoding these regions which specifically hybridize to the regions.

These arguments have been thoroughly reviewed but are deemed non-persuasive because they are allegations which are not supported by the level routine experimentation at the time of filing. As pointed out in the previous office action, in 1983 determination of hybridization conditions that allowed "specific hybridization" between nucleic acids which differed by only a few nucleotides was not routine. The methods at the time of the invention, such as Connor et al. Used short oligonucleotides (such as 19mers) under very high stringency hybridization conditions to differentiate alleles that different by only a few nucleotides. The specification only discloses two specific sequences for comparison to detect mismatches for use in making such short oligonucleotides. Furthermore, the specification teaches that under high "criterium" hybridization conditions the inserts of DR-beta-A,B,C and D cross hybridize with one another such that the scope of "specific hybridization is unclear. Further, the arguments are directed to embodiments to which the claims are not limited. The claims are very broadly drawn to any DNA sequence of an length that can hybridize to some unknown degree of specificity to the specific sequences of the specification. The claims are also drawn to sequences which portions containing any mismatch between these undiscovered hybridizing sequences. The locations, identities and sequences of these mismatch regions are unknown and completely unpredictable in light of the two specific sequences taught in the specification. The specification also does not provide guidance as to how to make sequences which "differ" from the specifically disclosed and the large number of "specifically hybridizing" sequences due to degeneracy of the genetic code. Therefore, this rejection is maintained.

5. Claims 17,17,20,22-42,44,46,47 and newly added claims 49 and 50 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of US Pat 5,169,941.

The response states that applicants will file a terminal disclaimer upon an indication of allowable subject matter. Consequently, the rejection is maintained.

NEW GROUNDS OF REJECTION

6. Figures 5-5D and 7-7A and the Brief Descriptions for these Figures are objected to because the Figures should instead be designated 5A-5E and 7A-7B, respectively.

7. Claims 16,17, 20, 23-42, 44, 46,47,49 and 50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are not enabled by the specification because the claims encompass DNA sequences of DR-beta-C and DR-beta-D which have not been taught in the specification. The specification states that a DR-beta-C and -D were isolated but does not disclose their sequence. The specification states that a clone containing DR-beta-C was deposited with the ATCC but the deposit has not been perfected. The skilled artisan would have no way of identifying a sequence as a DR-beta-C or -D sequence because the specification contains no description of it other than by this arbitrary name that provides no structural information. Consequently, a deposit of clones

containing these two sequences according to the requirements set forth in CFR 1.801-1.809 and amendment of the specification to the required statements regarding the deposit according to the rules is required.

8. Claims 16,17, 20, 23-42, 44, 46,47,49 and 50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 16, 17,20,23, 24,26-30,34-37,44,46,49 are indefinite because of the current "Markush" format. First, the claims are indefinite over the recitation "said sequence being selected from the group consisting of : (a) the DNA sequences of DR-B-A, DR-B-C and DR-B-C" because as written the claims are unclear as to whether "the DNA sequence" of (a) is a DNA sequence that contains all three of the sequences of DR-B-A, -B and -C or is a DNA sequence that can be any one of DR-B-A, -B or -C. The part of the rejection can be overcome by amending the claims to instead read "(a) the DNA sequence of DR-B-A, DR-B-B or DR-B-C". Similarly, the claim is further indefinite over recitation in part (b) of "the expressed portion of the DNA sequences of DR-B-A, DR-B-B and DR-B-C" because, again, the claim is unclear as to whether the DNA sequence of (b) includes expressed portions of all three or only one of DR-B-A, -B and -C.

(B) Claims 16, 17,20,23, 24,26-30,34-36,46,49 are indefinite over the recitation in part (e) of "DNA sequences which differ..." Because the claims are unclear as to whether "said DNA

sequence" is to contain multiples of the previously recited sequences or only one. The rejection can be easily overcome by amending the claims to instead recite "a DNA sequence which differs...".

C) Claims 31- 33,36,37,40-42,44,47,50 are indefinite over the recitation of "said polymorphic region being encoded by DNA selected from the group consisting of: (a) DNA sequences encoding....." Because the claims are unclear as to whether the DNA of the polymorphic region is multiple sequences encoding the recited amino acid regions or a single DNA sequence". This rejection an be easily overcome by amending "DNA sequences" and "portions" to "a DNA sequence" and "a portion".

D) Claims 34-37 are indefinite over the recitation of "said DNA inserts" because this term lack antecedent basis.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 23,24,26-29,31-33,36,37 are rejected under 35 U.S.C. 102(b) as being anticipated by Larhammer et al. (PNAS (JUNE 1982) 79: 3687-3691).

Larhammer et al. Teach a DNA sequence encoding an amino acid sequence of an HLA-beta chain locus. The nucleotide and predicted amino acid sequences are different from the

disclosed DR-B-A and DR-B-B sequences. However, because the intended meaning of the term "specifically hybridize" is unclear as discussed above, this DNA would be encompassed by the claims as written , i.e. "DNA sequences which specifically hybridize thereto", when the term is interpreted to mean specific hybridization to HLA-DR beta chains.

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 16,17,20,30,40,41,42,44,46,47,49,50 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 5,503,976. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of patent 5,503,976 are drawn to a specific embodiment, i.e. methods and kits using specific 19-mer oligonucleotides, which are encompassed in the more broadly drawn claims of the instant application.

13. No claims are allowable.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa Arthur whose telephone number is (703) 308-3988. The examiner can normally be reached on Monday-Wednesday from 8:00AM to 4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800

April 28, 1998